Longer Life Foundation

Final Report

Early-Adulthood Predictors of Mortality and Morbidity

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Abstract

Three publications have arisen from Longer Life Foundation grant 2015-008. In the first, using data from the Framingham Heart Study, we showed that as early as 28-38 years of age, almost 10% of variation in future lifespan can be predicted from simple clinical parameters. Specifically, we found diastolic and systolic blood pressure, blood glucose, weight, and body mass index (BMI) to be relevant to lifespan. These and similar parameters have been well-characterized as risk factors in the relatively narrow context of cardiovascular disease and mortality in middle to old age. In contrast, we demonstrated that such measures can be used to predict all-cause mortality from mid-adulthood onward. Further, we found that different clinical measurements are predictive of lifespan in different age regimes. Moreover, several of these parameters are best considered as measures of a rate of "damage accrual", such that total historical exposure, rather than current measurement values, is the most relevant risk factor (as with pack-years of cigarette smoking). Overall, simple physiological measurements have broader lifespan-predictive value than indicated by previous work; incorporating information from multiple time points can further increase that predictive capacity.

In the second, we examined the relationship between the length of an individual's life and the degree of good health that individual experiences. We conducted this work using longitudinal data from the nematode *Caenorhabditis elegans*. We used a custom culture apparatus to continuously monitor five aspects of aging physiology across hundreds of isolated individuals. Aggregating these measurements into an overall estimate of health, we found two chief differences between longer- and shorter-lived individuals. First, though long- and short-lived individuals are physiologically equivalent in early adulthood, longer-lived individuals experience a lower rate of physiological decline throughout life. Second, and counter-intuitively, long-lived individuals have a disproportionately extended "twilight" period of low physiological function. While longer-lived individuals experience more overall days of good health, their proportion of good to bad health, and thus their average quality of life, is systematically lower than that of shorter-lived individuals. Thus, within a homogeneous population reared under constant conditions, the period of early-life good health is comparatively uniform, and the most plastic period in the aging process is end-of-life senescence.

The methodologies developed for this above study were sufficiently novel as to warrant independent publication. The third published work arising from LLF funding was thus a detailed description of the custom culture apparatus mentioned above.

Publications Arising from LLF Funding:

1. Zhang WB & Pincus Z. Predicting all-cause mortality from basic physiology in the Framingham Heart Study. Aging Cell 15, 39–48 (2016). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4717277 (open access via NIH Pubmed Central)
2. Zhang WB, Sinha DB, Pittman WE, Hvatum E, Stroustrup N & Pincus Z. Extended Twilight among Isogenic C. elegans Causes a Disproportionate Scaling between Lifespan and Health. Cell Systems 3, 333–345.e4 (2016). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5111811 (open access via NIH Pubmed Central)
3. Pittman WE, Sinha DB, Zhang WB, Kinser HE & Pincus Z. A simple culture system for long-term imaging of individual C. elegans. Lab Chip 77, 71 (2017). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5675786 (open access available 2018-11-07)

(All cite “Longer Life Foundation grant 2015-008” in the funding acknowledgements section.)

Lay Summary

The primary outcomes from this LLF-funded work were described in two research publications.

In the first, we identified patterns in the way that human health changes from early adulthood to death, and used these patterns to define ways of predicting an individual's lifespan and future risk of disease. Clinically, early warning signs can be used to target individuals for additional care and intervention; actuarially, better predictors of lifespan and disease will enhance the ability of insurance pools to predict and manage risk.

Our analysis made use of data gathered by the long-running Framingham Heart Study, which was begun in 1948 and followed some 5,000 individuals throughout their lives. Only recently has enough of the original Framingham cohort deceased to enable this proposed work, which requires both many decades of historical data and knowledge of the ultimate lifespans of those involved.

In particular, we studied how changes in simple physiological values over time relate to future lifespan and health. Most "risk scores" combine multiple measurements (blood pressure, body mass index, etc.) made at one time to estimate the risk of a particular disease five or ten years hence. In contrast, we investigated how several years' or decades' worth of history of any given clinical measurement can predict lifespan twenty or more years in the future.

There are several ways in which knowing the history of a clinical measurement, in addition to its present value, might assist in predicting future lifespan. First, a measure's rate of change over time might predict risk better than its current value. This is the case with a skin blemish: a small but rapidly growing lesion is much more dangerous than a large yet stable one. Alternately, perhaps total cumulative historical exposure, rather than current status, is the best predictor. This is certainly the case for cigarette smoking, for example.

We thus examined whether different measurements, such as blood pressure, contribute to death and disease risk based only on their current value, cumulatively (like smoking), or only when changing (like skin blemishes). We found that blood pressure, body weight and body mass index, and blood glucose all act as cumulative risks. These results will enable better use of historical clinical data for longevity and disease risk estimation. Because such data are becoming increasingly available as part of routine practice due to the use of electronic medical records, our findings have immediate practical implications.

In the second publication, we addressed the question of how overall quality of life relates to total lifespan. That is, do longer-lived individuals live *better*, on average, than shorter-lived individuals? Or is extended lifespan intrinsically coupled to an extended period of late-life ill health? We had originally planned to address this question using the Framingham data by constructing a composite "frailty index" to measure an individual's quality of life over time.

To gain confidence in our mathematical methods, however, we decided to first apply them to much better-controlled studies of aging nematodes. These animals are often studied as a model of aging biology, and have very well-described stages of physiological decline (corresponding closely to the biology of human aging). We developed methods to measure relevant aspects of physiology in individual animals over their entire lifespan (movement rates, body size, and so forth). We then combined these measures to produce an overall index of good health, which we compared to lifespan.

From this work, we found that longer-lived individuals within a population do have more overall days of "good health" than their short-lived counterparts. However, the period of "ill health" was also extended in long-lived individuals, disproportionate to the increase in good health. That is, while long-lived individuals experience more "good" days, they experience *even more* "bad" days.

We are now exploring how best to translate these findings to humans, using the Framingham data as originally proposed.

Introduction

Overall, the goal of this project was to define how early-to-mid-life physiological measurements relate to future lifespan. In the original proposal, we aimed to examine this in the context of human clinical data. Using data from the Framingham Heart Study (FHS), we examined the relationship between physiological measurements in mid-life and future lifespan. For the proposed work on aggregating physiological measurements into an overall "health score" or "frailty index" in humans, we found it more productive to change scope to a better-controlled dataset derived from study of the model organism *C. elegans.* This allowed us to develop and validate our mathematical methods without concern for some of the confounds in using the FHS data (i.e. birth-cohort effects, changing medical technology throughout the almost 70 years of the study, and the ever-changing nature of the physiological parameters measured by the study).

The primary research results of the LLF-funded work have been published and area available in open-access format. The interested reader is recommended to examine those works (links provided above) to review the full results and methodological details. Note especially that the introduction and discussion sections of each were written to be accessible to a general audience. (Contact Zachary Pincus for reprints of the *Lab on a Chip* publication, a description of the *C. elegans* methods that we developed in the course of the funded work, if access to this journal is a problem.)

Relationship of Work to Original Proposal

The specific aims of the original proposal were as follows. The outcome of each aim is described.

Aim 1: Identify early predictors of mortality and specific morbidities.

Aim 1a: Determine the relationship between clinical parameters and future lifespan at the early FHS exams.

Outcome: this work was published as Zhang and Pincus, cited above.

Aim 1b: Determine the relationship between clinical parameters and specific late-life morbidities.

Outcome: we were surprised to find few robust correlations between any specific morbidities (as opposed to all-cause mortality) and mid-life clinical parameters, beyond recapitulating well-known cardiac disease risk factors. We found a number of weak correlations, but none that we judged to be worth detailed follow-up. We suspect that some of this issue was a matter of statistical power: our studies were able to detect correlations with all-cause mortality because we had a sufficient sample size when pooling across all ~1,300 individuals in our cohort. However, as fewer of those individuals had any specific morbidity, we were not able as easily distinguish signal from noise in these contexts.

Aim 1c: Create a composite "Frailty Index" as a predictor and an endpoint.

Outcome: as described above, we re-focused this sub aim from using the FHS data to using data generated in my lab using *C. elegans*. This allowed us to refine and validate mathematical methods using a more tractable dataset. This work was published as Zhang *et al.*, cited above.

Aim 2: Incorporate physiological history into mortality and morbidity risk predictions.

Outcome: this analysis was incorporated into Zhang and Pincus, cited above. (See lay summary above.)

Aim 3: Validate specific findings.

Aim 3a: Replicate initial findings using other cohorts within the FHS.

Aim 3b: *Replicate initial findings using independent data.*

Outcome: both of these efforts remain ongoing.

Discussion and Future Plans

Our findings in *C. elegans* are provocative but call out for extension in several directions, which are described below. Our findings from the FHS data are more self-contained, but still require independent validation, which (as above), we are still investigating.

Our chief future aim is to translate the results of Zhang *et al.* in *C. elegans* to humans using the FHS data, as originally proposed in Aim 1c. As described above, we found that longer-lived *C. elegans* within a population spend an increased fraction of their lives in poor health, compared to shorter-lived individuals.

We would like to ask this same question in humans. Now that we have developed mathematical methods for aggregating physiological measurements into a quantitative “health score” in *C. elegans*, we expect that it should be plausible to apply these same methods to the FHS data. This will be the subject of an upcoming NIH grant application, in collaboration with a clinical researcher who is expert in constructing “frailty indices” from human datasets.

We also aim to understand the genetic mechanisms underlying our *C. elegans* findings. Our initial studies focused on the differences between long- and short-lived individuals in a wild-type population. However, there are many well-studied long- and short-lived mutant strains. We thus aim to investigate the relationship between lifespan and health in these mutants, to determine whether these strains fall along the same continuum we identified in wild type (long life brings a relatively extended senescence), or whether some mutations fundamentally alter the relationship between life and health. This work is the subject of a current NIH application.